



JULY 2006

UPDATE

National Toxicology Program

Headquartered at the National Institute of Environmental Health Sciences NIH-DHHS

NTP Update Distribution Goes Electronic in October

Important Notice

NTP Update will go paperless beginning with the October 2006 issue. Starting in October, the NTP will make its quarterly newsletter available electronically either from the NTP website or through its electronic email notification listserv. Distribution of the newsletter by mail will end. The NTP invites anyone who currently receives the *NTP Update* by mail to sign-up to get the newsletter electronically through the NTP listserv. Just register for the listserv through the NTP website (see "Receive News by email") or send an email to ntpmail-request@list.niehs.nih.gov with the word *subscribe* as the body of the message. This service is free-of-charge. We look forward to continuing to bring you news about NTP activities and events.

NTP Host Susceptibility Program

Each year, many new substances are introduced for use in such everyday items as foods, personal care products, prescription drugs, household cleaners, and lawn care products. We do not know the effects of many of these substances on our health, yet we may be exposed to them while manufacturing, distributing, using, and disposing of them or when they become pollutants in our air, water, or soil. The NTP is launching a new program under the direction of Dr. John Pritchard, NIEHS, to try and tease out potential genetic differences in susceptibility that may lead to a better understanding about why substances in our environment may become hazardous to humans. This new host susceptibility program (HSP) will provide the NTP with a mechanism for planning, conducting, and analyzing multi-strain assessment of chemical toxicity. The NTP's traditional testing program evaluates substances in F344 rats and/or B6C3F1 mice. Through the HSP, the NTP will take known chemicals identified as toxicants in its rodent testing program and evaluate them in multiple mouse strains to see which strains are particularly sensitive or insensitive to the chemicals causing toxicity. This initial screening will provide a basis for further study through the NIEHS intramural and/or extramural programs to identify the specific genes that confer sensitivity or resistance to the toxicity. Ultimately, the NTP hopes to learn more about the key genes and pathways involved in the toxic response and the etiology of diseases mediated by substances in our environment. Such understanding will ultimately lead to more specific, targeted testing strategies for the NTP to use for predicting the potential toxicity of substances we encounter in our daily lives.

2006 NIH Research Festival

NIEHS/NTP staff has been chosen to present a special symposium, *Benefits and Risks of ART in Preventing Mother-to-Child Transmission of HIV*, at the 2006 NIH Research Festival on October 17-20, 2006, at the Natcher Conference Center, NIH in Bethesda, MD. The symposium will review the clinical benefits of antiretroviral therapy (ART) in reducing mother-to-child transmission of HIV along with describing the results of NIEHS/NTP studies of mitochondrial dysfunction, tumor reduction, and biomarkers of genetic damage in rodents exposed *in utero* and postnatally to Zidovudine (ZDT), an ART drug. In addition, talks will cover studies of infants born to HIV-infected women and exposed to ART with special consideration given to implications of the findings for the long-term health of these children. Staff presenting at the symposium include Drs. John Bucher, William Copeland, and Robert Sills, and Ms. Kristine Witt. The exact day and time for this symposium is not yet set. The festival is open to the public and additional information, including the calendar of events, is posted on the NIH website (<http://researchfestival.nih.gov/>).

(Continued next page)

Symposium Notice

The NIEHS/NTP staff will also present the talks being given at the NIH Research Festival on September 28, 2-4 PM, in the Rodbell Conference Center, Building 101, at the NIEHS. Persons planning to attend this symposium should review access and parking information for the NIEHS campus on the website:

<http://www.niehs.nih.gov/external/south.htm#security>.

Contact Information: Denise Lasko, NTP Liaison and Scientific Review Office, NIH/NIEHS P.O. Box 12233, MD A3-01, Research Triangle Park, NC, 27709; phone: 919-541-0255; lasko@niehs.nih.gov

SACATM Teleconference in August

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) will hold a teleconference on Thursday, August 3, 2006, from 1-4 PM. SACATM will discuss the conclusions and recommendations of a peer review panel convened on May 23, 2006 to evaluate the validation status of two *in vitro* basal cytotoxicity test methods for estimating starting doses for acute toxicity:

(<http://iccvam.niehs.nih.gov/methods/invidocs/panelmeet/meetinfo.htm>).

The expert panel peer reviewed the background review document on the *in vitro* 3T3 and NHK cytotoxicity test methods and evaluated the extent to which established validation and acceptance criteria had been adequately addressed for the intended purpose of the test methods. The peer review panel also provided comments on draft Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) recommendations regarding the proposed use of these test methods, draft

test method protocols, draft performance standards, and draft recommended future studies. SACATM's comments on the peer review panel's conclusions and recommendations will be provided to ICCVAM for consideration during finalization of ICCVAM test method recommendations.

The teleconference will be public with an opportunity for public comment. The agenda and additional background materials will be posted on the NTP website prior to the meeting (<http://ntp.niehs.nih.gov>, see "Calendar of Upcoming Events") or can be obtained by contacting the Executive Secretary, Dr. Kristina Thayer. This meeting is also being announced in the Federal Register.

Contact Information: Dr. Kristina Thayer, Executive Secretary, NTP Liaison and Scientific Review Office, NIH/NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, NC 27709; phone: 919-541-5021; thayer@niehs.nih.gov

NTP Technical Reports Review Subcommittee

The NTP Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors is scheduled to meet on August 28, 2006, at the NIEHS, 111 T.W. Alexander Dr. Research Triangle Park, NC. The subcommittee will peer review the findings and conclusions from NTP studies in genetically modified models reported in draft NTP Technical Reports. The subcommittee will also discuss the utility of genetically modified models for cancer hazard identification.

The draft reports tentatively scheduled for review are:

Allyl bromide	Glycidol
Benzene	Phenolphthalein
Dicyclohexylcarbodiimide	

Details about this meeting will be announced in the Federal Register and posted on the NTP website (<http://ntp.niehs.nih.gov/> see *Calendar of Events*) or can be obtained by contacting the Executive Secretary, Dr. Barbara Shane. This meeting is open to the public and public comment, both written and oral, is welcome on any report.

The subcommittee met on June 12 at the NIEHS to peer review four draft NTP Technical Reports including a multigenerational study on genistein. The subcommittee unanimously accepted the conclusions for all reports (see "Latest News" on the NTP homepage). Actions from this meeting will go to the NTP Board of Scientific Counselors for approval after which the NTP will make any necessary revisions prior to finalizing and publishing the reports. Minutes will be prepared and posted in the near future.

All final NTP Technical Reports are available electronically on the NTP website (<http://ntp.niehs.nih.gov/index.cfm?objectid=7DA86165-BDB5-82F8-F7E4FB36737253D5>) or in hardcopy by contacting Central Data Management (919-541-3419 or CDM@niehs.nih.gov).

Contact Information: Dr. Barbara Shane, Executive Secretary, NTP Liaison and Scientific Review Office, NIH/NIEHS, P.O. Box 12233, MD A3-01, Research Triangle Park, NC 27709; phone: 919-541-4253; shane@niehs.nih.gov

NTP Biomarkers Workshop Scheduled for September

For more than a quarter century, the NTP testing program has provided extensive and useful scientific information for predicting human health hazards and protecting public health. The NTP periodically conducts reviews of models used in its testing program to analyze critically their predictive power and determine whether study protocols should be altered. As part of this effort, the NTP is convening a workshop titled *Biomarkers for Toxicology Studies* that will be held on September 20-21, 2006, at the National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive, Research Triangle Park, NC 27709.

The workshop's overall goal is to identify biomarkers for carbohydrate/lipid metabolism and lung and cardiac function and evaluate their utility for inclusion in rodent

toxicology studies to better characterize endpoints of environmentally induced diseases or biological processes related to disease etiology.

This workshop is open to the public with time set aside in the agenda for public comments during plenary on the first day. The public can also attend the breakout groups as observers. Information about the workshop and on-line registration are available from the NTP website: <http://ntp.niehs.nih.gov/> see *Calendar of Events*)

Contact Information: Denise Lasko, NTP Liaison and Scientific Review Office, NIH/NIEHS P.O. Box 12233, MD A3-01, Research Triangle Park, NC, 27709; phone: 919-541-0255; lasko@niehs.nih.gov

Workshop Summary: Hormonally Induced Reproductive Tumors – Relevance of Rodent Bioassays

On May 22-24, 2006, the NTP held the workshop, *Hormonally Induced Reproductive Tumors - Relevance of Rodent Bioassays*. Its overall objective was to determine the adequacy and relevance to human disease outcome of rodent models for four types of hormonally induced reproductive tumors (ovary, mammary gland, prostate, and testis). The format included both plenary talks and tumor-site-specific breakout groups.

In brief, none of the breakout groups felt the current NTP models are completely sufficient for predicting human disease outcomes and adequate models do not exist in general for some tumor types. All breakout groups suggested that the NTP consider modifying its testing protocols (i.e., age at exposure, length of study, additional endpoints, etc.) and/or using alternative models (i.e., transgenics, *in vitro*, etc.) to improve sensitivity. Breakout group reports and additional

information on the workshop, including participants, presentations, public comments and background materials, are posted on the NTP website.

This workshop is one in a series being held in conjunction with implementation of the NTP Roadmap (<http://ntp.niehs.nih.gov/go/vision>). The overall purpose of the series is to examine the NTP's current testing strategies and identify ways to improve the ability of the NTP bioassays to identify substances that may pose carcinogenic or other health hazards for humans. A future workshop (see above) will address biomarkers for carbohydrate/lipid metabolism and lung and cardiac functions.

Contact Information: Dr. Paul Foster, NIH/NIEHS, P.O. Box 12233, MD EC-34, Research Triangle Park, NC, 27709; phone: 919-541-2513; foster2@niehs.nih.gov

Upcoming Events

August 3, 2006	Teleconference: The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM): 1:00-4:00 PM
August 28, 2006	NTP Board of Scientific Counselors Technical Reports Review Subcommittee Meeting, NIEHS, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709
September 20-21, 2006	NTP Workshop: <i>Biomarkers for Toxicology Studies</i> , NIEHS, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709
September 28, 2006	NTP Symposium: <i>Benefits and Risks of ART in Preventing Mother-to-Child Transmission of HIV</i> , NIEHS, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709
October 17-20, 2006	NIH Research Festival, Natcher Conference Center, NIH in Bethesda, MD http://researchfestival.nih.gov/default.htm

Center for the Evaluation of Risks to Human Reproduction (CERHR)

Genistein and Soy Formula Expert Panel Reports Available for Public Comment

CERHR held an expert panel meeting on genistein and soy formula on March 15-17, 2006, in Alexandria, VA. An independent panel of 14 scientists evaluated information on human exposure, reproductive toxicity, and developmental toxicity of genistein and soy formula.

The final expert panel reports are now available on the CERHR website (<http://cerhr.niehs.nih.gov>) and in hardcopy or on CD from CERHR (contact information below). Public comments received on these reports will be posted on the CERHR website and included in the NTP-CERHR Monograph for each substance. The NTP will consider all public comments during preparation of the NTP Briefs on these substances.

Draft NTP Brief on Di-(2-ethylhexyl)phthalate (DEHP)

On October 10–12, 2005, an expert panel conducted an updated evaluation of the potential reproductive and developmental toxicities of DEHP. Following conclusion of the public comment period on the expert panel report,

CERHR staff prepared the draft NTP Brief on DEHP. The draft DEHP Brief is now available on the CERHR website (<http://cerhr.niehs.nih.gov>) and in hardcopy or on CD from CERHR (contact information below). Comments invited through the Federal Register (71(107) pp.32365–32366) will be posted on the CERHR website and considered during finalization of the NTP Brief for DEHP.

Hydroxyurea and Bisphenol A Expert Panel Meetings Planned

Expert panel meetings on hydroxyurea and bisphenol A are being planned for 2007. Draft expert panel reports, information about submitting public comments, and details about the meetings will be announced later this year.

Contact Information: Dr. Michael D. Shelby, Director CERHR, NIH/NIEHS, P.O. Box 12233, MD EC-32, Research Triangle Park, NC 27709; phone: 919-541-3455; shelby@niehs.nih.gov

NTP Interagency Center for the Evaluation of Alternative Toxicology Methods (NICEATM)

Final Evaluation Report on *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants

NICEATM announces availability of the report, *ICCVAM Test Method Evaluation Report: In Vitro Ocular Toxicity Test Methods for Identifying Severe Irritants and Corrosives*. The report provides recommendations on the use of four *in vitro* test methods in a tiered-testing strategy, where positive substances can be classified as ocular corrosives or severe irritants. The four ocular toxicity test methods evaluated are:

- Bovine Corneal Opacity and Permeability test
- Isolated Chicken Eye test
- Isolated Rabbit Eye test
- Hen's Egg Test – Chorioallantoic Membrane

The report includes (a) ICCVAM's final test method recommendations on the use of these four *in vitro* test methods, (b) test method protocols for their use, (c) recommended future optimization and validation studies, (d) reference substances for such studies, and (e) overall recommendations related to all four *in vitro* test methods. Additionally, NICEATM announces the availability of the Background Review Documents for each test method. These documents are available electronically on the NICEATM/ICCVAM website (<http://iccvam.niehs.nih.gov>) and in hardcopy by contacting NICEATM (contact information below).

Evaluation of *In Vitro* Testing Methods for Estimating Acute Oral Systemic Toxicity

NICEATM held a public, scientific peer review meeting to evaluate the validation status of the *in vitro* 3T3 and normal human keratinocyte (NHK) neutral red uptake (NRU) basal cytotoxicity test methods for estimating starting doses for *in vivo* acute oral toxicity tests. The meeting was held on May 23, 2006, at the National Institutes of Health (NIH), Natcher Conference Center.

These two *in vitro* cytotoxicity test methods are proposed as adjuncts to the *in vivo* acute oral toxicity tests to refine (i.e., to lessen or avoid pain and distress) and/or reduce animal use. At this meeting, an independent scientific panel considered the background review document on the 3T3 and NHK cytotoxicity test methods, evaluated the extent that the document addresses established validation and acceptance criteria, and commented on the draft ICCVAM recommendations for the proposed use of these test methods, the draft test method protocols, and the draft performance standards.

The panel determined that, in general, the background review document is adequate and sufficient, but noted some minor deficiencies and recommended some additional analyses although none of these deficiencies was determined to affect ICCVAM's recommendations.

The panel agreed that the applicable validation criteria are adequately addressed for using these *in vitro* test methods in a weight-of-evidence approach to determine the starting dose for acute oral *in vivo* toxicity protocols. Once the panel's report is published, its availability will be announced in the Federal Register and the report will

be posted on the NICEATM/ICCVAM website (<http://iccvam.niehs.nih.gov>).

Contact Information: Dr. William S. Stokes, Director NICEATM, NIH/NIEHS, P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709, phone: 919-541-2384; iccvam@niehs.nih.gov

The NTP Testing Program

Request for Study Nominations

With a broad mandate to provide toxicological characterizations for chemicals and other agents of public health concern, the NTP accepts nominations for new toxicological studies at any time. Labor unions, academic scientists, federal and state agencies, industry, and the general public are welcome to make nominations for specific substances or for general issues related to potential human health hazards of occupational or environmental exposures. As available, a rationale should accompany the nomination along with background information describing sources of exposure and possible adverse health effects or concerns associated with exposure, the chemical name and the Chemical Abstract Service (CAS) registry number. Details about the nomination process are available on the NTP website ([http://ntp.niehs.nih.gov/select Nominations to the Testing Program under Testing Information](http://ntp.niehs.nih.gov/select/Nominations%20to%20the%20Testing%20Program%20under%20Testing%20Information)) or by contacting the NTP Office of Chemical Nomination and Selection (contact information below).

Current areas of focus in the NTP's testing program include potential hazards associated with nanoscale materials, perfluorinated compounds, herbal dietary supplements, photoactive chemicals, flame retardants, certain complex occupational exposures, dioxin-like compounds, contaminants of finished drinking water,

and endocrine-disrupting substances, and methods for assessing potential cardiac toxicity.

All nominations undergo several levels of review before being selected by the NTP for study. These steps of review help to ensure that the NTP's testing program addresses toxicological concerns pertinent to all areas of public health and help maintain balance among the types of substances and issues evaluated. Studies are initiated on selected nominations as time and resources permit.

Study Nominations Currently in Review

A group of 10 new study nominations is currently being considered for new toxicological studies within the NTP's testing program (<http://ntp.niehs.nih.gov/go/21158>). The NTP Board of Scientific Counselors reviewed these nominations at its June 13, 2006 meeting (<http://ntp.niehs.nih.gov/go/9741>). The NTP website also provides access to electronic versions of supporting documents for each nomination and further information on the NTP Study Nomination Review and Selection Process.

Contact information: Dr. Scott Masten, Office of Chemical Nomination and Selection, NIH/NIEHS, P.O. Box 12233, MD A3-07, 111 T.W. Alexander Dr., Research Triangle Park, NC 27709; phone: 919-541-5710; masten@niehs.nih.gov